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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
07/402,450	09/01/1989	GEORGE J. MURAKAWA		8131

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
MILLER, MARINA I	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	07/402,450	MURAKAWA ET AL.	
	Examiner	Art Unit	
	Marina Miller	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2005 and 15 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *114-234* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *114-234* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/29/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *1 copy*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' submissions filed on 11/29/2005 and 12/15/2005 is acknowledged.

Claims 114-234 are pending.

Claims 1-113 are cancelled.

Claims 114-234 presently are under examination.

Applicants' arguments have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are applied.

Information Disclosure Statement

The Information Disclosure Statement (IDS) filed 11/29/2005 has been considered in full.

Priority

U.S. applications 07/355,296 ('292 application) filed 05/22/1989; 07/143,045 ('045 application) filed 01/12/1988; and 07/148,959 ('959 application) filed 01/27/1988 do not provide support for newly filed claims 114-234.

Applicants argue that the priority applications '045 and '959 provide support for the claimed invention. The examiner reviewed the priority applications, but did not find the support for the claimed method, composition, and kit. For example, '959 application does not disclose a reference RNA comprising an insertion/deletion of any size and determining the amount of a target RNA from the amplified amount of any reference RNA. The specification of '959 application discloses a reference RNA ("maxigene") formed by a multi-base pair insert into the RNA of 22 bases (p. 3-4). Further, '959 application does not disclose a multi-base pair

"deletion," but only discloses "insert." '959 application does not disclose the amplification of a reference RNA for the quantification purpose using any unspecified primers, but only discloses "a reference RNA which can be amplified and detected by the same oligonucleotides used for authentic virus RNA samples" (p. 3). '959 application does not disclose a composition and a kit comprising a known quantity of a reference RNA sequence with an unspecified multibase insert/deletion and primers for the amplification and/or reverse transcription of the reference RNA. '959 application only discloses an insertion of 22 bases and primers that are used for the amplification of both a target and a reference RNA and "kits" that include self-contained appropriate quantities of primers and probes (p. 3, 7).

Similarly, '045 application does not disclose a reference RNA comprising an insertion/deletion of any size and determining the amount of a target RNA from the amplified amount of any reference RNA. The specification of '045 only discloses " a small insertion," but not a deletion (p. 8). The specification of '045 also discloses only amplification with the same primers of both a target and a reference RNA (p. 8).

If applicant desires benefit of the provisional applications '045 and '959, applicant is invited to point to specific support by page and line number for each limitation of the instant claims in the provisional applications mentioned above. Thus, priority for claims 114-234 is granted only to the filing date of the instant application filed 09/01/1989.

Affidavit under 37 CFR 1.131 and 1.132

The Declarations under 37 CFR 1.132 by John Rossi which were filed 6/4/2004 and 11/29/2005 have been fully considered.

The Declaration under 37 CFR 1.131 by the inventors, George Murakawa, Bruce Wallace, John Zaia, and John Rossi, which was filed 12/15/2005, was fully considered. The Declaration asserts that the date of conception of the instant invention is prior to 21 August 1989. As the prior art cites below was published in 1988, the Declaration filed 12/15/2005 does not apply to the instantly cited prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 114-234 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Newly added claims 114-234 are directed to a method, amplification and reverse transcription mixtures, and a kit for quantitation of a target viral RNA in a sample. However, the limitations recited in claims 114-234 do not have support in the specification, claims, or drawings, as originally filed. Specifically, the instant claims recite a reference RNA sequence consisting/comprising a selected viral RNA sequence with a multibase insert/deletion. The original application does not have support for a reference RNA comprising an insertion/deletion of any size. The specification discloses that "a reference RNA may be a "minigene" or a "maxigene" formed by a multi-base pair insert into or deletion of at least about 20 nucleotides

from a unique site." P. 6. Further, the original specification discloses that "a small insertion" is cloned into a viral RNA used as an internal standard (p. 7, lines 9-19). Thus, the instant claims reciting a reference RNA with an insertion of an unspecified length do not have support in the originally filed application.

Further, claims 114-145, 152-183, and 190-225 recite determining the amount of a target viral RNA present in a sample before amplification from the amount of the reference RNA before and after the amplification. The original specification discloses "[b]ecause the quantity of 'maxigene' or 'minigene' RNA originally included in the application reaction is known, the amount of signal obtained from the maxi or minigene amplified product can be related to the signal obtained from the patient sample." (p. 7, lines 2-8). The originally filed application does not provide support for quantifying target RNA wherein a reference and a target RNA are amplified at different rates (*e.g.*, an amplified target and a reference RNA have significantly different length). The specification supports only quantifying target RNA wherein a target and a reference RNA have similar length, *i.e.*, "maxi" or "minigenes" about 20 bases longer/shorter than a target RNA, as set forth above. Thus, the original application does not support determining the amount of a target RNA from the amplified amount of any reference RNA (*i.e.*, a reference RNA significantly different in length than the target).

Claims 114-234 recite the amplification of a target viral RNA and a reference RNA "under conditions appropriate to simultaneously amplify" both RNAs. "Appropriate conditions" for the amplification comprise, among other parameters, a structure of amplification primers. Claims 146-151, 184-189, and 226-234, directed to a composition and a kit, specifically recite amplification primers for amplifying a target and a reference RNA. However, the originally filed

application does not have support for a primer pair which may be "appropriate" for amplifying both RNAs wherein a target and a reference RNA are amplified at different rates (*e.g.*, wherein RNAs amplified with the primers are significantly different in length). The specification discloses that "[a]n additional aid to quantitation of virus levels in patient samples is provided by a reference RNA which can be amplified and detected by the same oligonucleotides used for authentic virus RNA samples." (p. 6, emphases added by the examiner) This can only occur when the RNAs amplified by the disclosed primers are similar in length. Thus, the original disclosure does not support using a primer pair for amplifying both RNAs wherein the amplification substrates (RNAs) are significantly different.

Claims 146-151, 184-189, and 226-234 recite amplification and reverse transcription reaction mixtures and a kit for quantitation of a target viral RNA in a sample. The original application does not have support for a composition and a kit comprising a reference RNA sequence comprising any multibase insert/deletion. Further, the original disclosure does not have support for a mixture and a kit comprising a primer pair for quantifying a target RNA wherein a target and a reference RNA is amplified at different rates (*e.g.*, RNAs amplified with the primers are significantly different in length). The specification only discloses an insertion/deletion of about 20 bases and primers that are used for the amplification of both a target and a reference RNA, as set forth above. The specification also only discloses primers that provide similar amplification rate of both RNAs (p. 6).

For these reasons, the claims are rejected for reciting new matter.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentations is "undue." These factors include, but are not limited to:

a) The breadth of the claims;
b) The nature of the invention;
c) The state of the prior art;
d) The level of one of ordinary skill;
e) The level of predictability in the art;
f) The amount of direction provided by the inventor;
g) The existing of working examples; and
h) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. 858 F.2d at 740. While all of these factors are considered, sufficient amount for a prima facie case are discussed below.

Claims 114-234 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for quantitation of a target viral RNA using a reference RNA comprising an insert of about 20 bases such that same amplification primers can be used for both RNAs, does not reasonably provide enablement for quantitation of a target RNA wherein a reference and a target RNA are significantly different lengths such that the two RNAs would be

amplified at different rates. The specification also does not provide enablement for primers that amplify a target and a reference RNA at different rates (*e.g.*, wherein amplified portions of a target and a reference RNA are significantly different lengths). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a) The claims are broad because they are drawn to a method, a composition, and a kit for quantitation of a target viral RNA in a sample comprising a reference RNA with an insert/deletion of unspecified length and generic primers "appropriate" for amplifying both RNAs. The specification does not provide specific guidance to practice the invention wherein a target and a reference RNAs are significantly different lengths so that the amplification rates of RNAs are expected to be different. The specification also does not provide specific guidance to practice the invention wherein primers produce amplified portions of a target and a reference RNAs of significantly different lengths such that the amplification rate of RNAs is expected to be different. Because the rates of the amplification of a target and a reference RNA are different under those conditions, the determination of the amount of a target RNA from the amount of a reference RNA before and after the amplification would not be able to be determined with any degree of accuracy.

b) The invention is drawn to a method a composition, and a kit for quantitation of a target viral RNA.

c), e) Prior art discloses amplification of a reference and a target RNA wherein the two are not significantly different lengths, and are therefore amplified at similar rates. *See* Murakawa, *DNA*, 7(4):287-295; Zaia, *Testtrends*, 3(1):4-5 (1 June 1989); Chelly, *Nature*, 333:858-860 (30

June 1988). Prior art further discloses that the efficiency of PCR is affected by many different factors, for example, the length and secondary structure of a nucleic acid and a type of primers. *See* Diaco, *PCR Strategies*, Practical Considerations for the design of quantitative PCR assay, Academic Press, Inc., ed. Innis et. al., ch. 7, p. 84-108 (1995). Prior art discloses that it is a disadvantage to rely on different primer sequences and suggests using a target and a reference RNAs similar in length and composition and using the same amplification primers. *Id.* at 97.

d) The skill of those in the art of molecular biology and bioinformatics is high.

f) The specification does not provide guidance how to make and use the invention for quantifying a target viral RNA using a reference RNA which is significantly different in length nor for use of generic primers wherein the amplification rates for the two RNAs are different.

g) The specification provides working examples for amplification of a target viral RNA, but does not provide an example of quantifying a target RNA using a reference RNA.

h) In order to practice the claimed invention, one skilled in the art must randomly select an insertion/deletion in a reference RNA and must guess which parameters to use for an "appropriate" amplification of both RNAs so that the efficiency of the amplification, which is affected by many factors, is similar for the two RNAs. This constitutes undue experimentation.

Due to the undue experimentation required to obtain the goal of the invention, the lack of directions presented in the specification, the complex nature of the invention, and the state of the prior art, the specification fails to teach one skilled in the art how to use the claimed method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 146-151 and 229-234 are rejected under 35 U.S.C. 102(a) as being anticipated by Murakawa, *DNA*, 7(4):287-295 (1988).

Murakawa discloses amplification and reverse transcription reaction mixtures comprising a target viral RNA, a known quantity of a reference RNA with an insert, and a primer pair for a target and a reference RNA and a kit comprising a reference RNA and a primer pair (p. 288-289, Material and Methods), thereby anticipating the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 114-145 and 190-228 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murakawa, *DNA*, 7(4):287-295 (1988), in view of Chelly, *Nature*, 333:858-860 (30 June 1988).

Murakawa discloses detection of HIV-1 RNA in patient samples (abstract). Murakawa discloses reverse transcription and amplification of RNA (p. 288). Murakawa discloses selecting a sequence present in a target viral RNA (fig. 1). Murakawa discloses a reference RNA consisting of the selected target RNA and an insertion of 21 bases (p. 292, fig. 7-8). Murakawa discloses adding a known quantity of a reference RNA to a sample (5.0 ng; p. 293, fig. 8 or

equimolar amount, p. 292). Murakawa discloses comparing intensities of bands corresponding to amplified products of a sample and a reference (*i.e.*, comparing the amount of an amplified target and a reference RNA) (fig. 7-8 and p. 292, right col.). Murakawa discloses a target and a reference RNA are amplified with equivalent efficiencies (fig. 7 and p. 292, right col.). Murakawa discloses T7 RNA polymerase (p. 288). Murakawa disclose labeled probes (isotope) (p. 289).

Although Murakawa discloses comparing the amount of RNAs after the amplification, Murakawa does not specifically disclose measuring the amount of RNA and determining the amount of a target RNA before amplification from the amount of a reference RNA.

Chelly discloses a method for quantifying a target RNA (dystrophin transcript) from the amount of a reference RNA (aldolase transcript) (abstract). Chelly discloses adding a reference RNA to a sample (p. 858). Chelly discloses measuring the amount of an amplified product using labeled primers and electophoresis (top of p. 859, right col. and fig. 2-3). Chelly discloses that "the starting material [dystrophin] could be quantified." (p. 859). Chelly discloses formula $Y=A(1+R)^n$ (proportion I)wherein Y and A are the amount of RNA before and after the amplification, R is the efficiency, and n is the number of cycles (p. 859). If Y and A of a reference are known, the target and the reference RNA are amplified at the same rate, and the amount of amplified target RNA is determined (*e.g.*, by using labeled primers or electrophoresis, as taught by Chelly), then the amount of the target RNA before the amplification is calculated from proportion I.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method Murakawa to determine the starting amount of a target RNA,

such as taught by Chelly, where the motivation would have been to determine the presence and/or abundance of a virus in a sample, as taught by Chelly, p. 858.

Claims 152-189 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murakawa, *DNA*, 7(4):287-295 (1988), in view of Chelly, *Nature*, 333:858-860 (30 June 1988), as applied to claims 114-145 and 190-228 above, and further in view of Arya, PNAS, 84:5429-5433 (1987).

Murakawa and Chelly make obvious the method of claims 114-145 and 190-228, as set forth above. Murakawa also teaches the amplification and the reverse transcription reaction mixtures comprising a target viral RNA, a known quantity of a reference RNA with an insert, and a primer pair for a target and a reference RNA and the kit comprising a reference RNA and a primer pair amplification of claims 146-151 and 229-234, as set forth above.

Murakawa and Chelly do not disclose a reference RNA with deletion.

Arya discloses constructing clones comprising deletion variant of a viral (HIV) nucleic acid (p. 5431, fig. 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method, mixture, and the kit of Murakawa and Chelly to use deletion variants of a target RNA, such as taught by Arya, where the motivation would have been to find a reference RNA with the amplification efficiency similar to that of a target RNA, as taught by Chelly, p. 860.

Answer to applicants' arguments.

Applicants submitted comments concerning references listed in IDS, and specifically Murakawa, *DNA*, 7(4):287-295 (1988) and Chelly, *Nature*, 333:858-860 (30 June 1988).

Applicants argue that Murakawa does not disclose adding a known amount of a reference RNA to a sample containing a target viral RNA sequence, measuring the amount of amplified products, and quantifying a target RNA.

In response to applicants' arguments, it is noted that Murakawa discloses adding a reference RNA to a sample. Specifically, 50 ng of PGM92+21 is added to viral RNA prepared from blood and amplified for 15 cycles (fig. 8). Also, an equimolar amount of RNA from PGM92+21 (reference) was added to pGM92 (a sample comprising a selected target viral RNA) (fig. 7 and p. 292). Although Murakawa does not teach measuring the amount of amplified products, and quantifying a target RNA, Chelly does teach these limitations, as set forth in the rejection above.

Applicants also argue that Chelly does not teach adding a known amount of a reference RNA to a sample and measuring and quantifying the precise amount of a target.

In response to applicants' arguments, it is noted that Chelly discloses measuring the amplification products and quantifying the starting amount of a target RNA, as set forth in the rejection above. Specifically, Chelly discloses measuring the amount of amplified product by using, for example, labeled primers (p. 859), quantifying the starting material (p. 859), and a simple mathematical equation for calculating the amount of RNA (p. 859).

Motivation to combine references is provided in the rejection above. Thus, the rejection over Murakawa and Chelly provided above, is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marina Miller whose telephone number is (571)272-6101. The examiner can normally be reached on 8-5, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph. D. can be reached on (571)272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marina Miller
Examiner
Art Unit1631

MM

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran
2/28/06